RELATIONSHIPS BETWEEN HYPERURICEMIA AND GOUT, HEREDITARY AND BEHAVIOR FACTORS-SPECIAL EMPHASIS ON ROLE OF ACUTE AND CHRONIC PHYSICAL EXERCISE

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RELATIONSHIPS BETWEEN HYPERURICEMIA AND GOUT, HEREDITARY AND BEHAVIOR FACTORS, AND CARDIOVASCULAR DISEASE — WITH SPECIAL EMPHASIS ON THE ROLE OF ACUTE AND CHRONIC PHYSICAL EXERCISE

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ABSTRACT

Numerous factors can influence serum uric acid concentration in healthy individuals: genetic factors, age and sex, body type, drugs, diet, occupation and social class status, achievement-oriented behavior and drive, acute physical exercise and chronic physical exercise. Statistical studies on monozygotic and dizygotic twin pairs have suggested that in males the mechanisms controlling the normal serum uric acid levels are influenced more by environmental factors whereas in females, hereditary factors predominate. Significantly higher mean serum uric acid values have been reported in both high school and college athletes when contrasted with comparably aged samples from "normal" populations. Three factors have been suggested which, singly or in combination, may contribute to high serum uric acid values in athletes: (a) acute and/or chronic physical exercise, (b) genetic predisposition, and (c) achievement-oriented behavior. Some epidemiological studies report significant but low positive correlations between high serum uric acid levels and psycho-social characteristics such as intelligence, *achieved* social status, and "drive," but it is still not clear whether they reflect *inherent* personal characteristics, environmental factors, e.g., participation in athletics or both. The increase in serum uric acid with acute physical exercise is well documented. The causal relationship between muscular exercise and elevated serum uric acid is still not clear, but inhibition of uric acid excretion with a corresponding rise in its concentration in the blood is the most probable explanation. The effects of chronic physical exercise (training) on serum uric acid have not been studied systematically. Strenuous conditioning (a season of competitive water polo) has been shown to *decrease* significantly the mean serum uric acid value of a sample of college athletes. Probable explanations for this result are (a) a relatively constant turnover of urate accompanied by a progressively increasing plasma volume and/or (b) an absolute increase in uric acid excretion.

INTRODUCTION

Many factors influence serum uric acid concentration in healthy people: age and sex (44), body type (18), drugs (19), diet (38), occupation and social class status (13), achievement-oriented behavior and drive (7), acute physical exercise (39, 54) chronic physical exercise (4, 42) and genetic factors (44, 59).

The relationship between serum uric acid concentration, gout, and gouty arthritis has been under investigation for almost 200 years (59) but only recently has hyperuricemia been reported to be associated with coronary heart disease (18, 22, 45), hypercholesterolemia (24), hypertriglyceridemia (2) and hypertension (6, 10) with much greater frequency than in the general population.

Older studies have shown that acute physical exercise of various intensity and duration produced a rise in serum uric acid concentration in both men (39) and women (54). More recently, a positive relationship in male high school students was found between serum uric acid concentration and the degree of participation in combined scholastic and athletic activities (13). In another study, healthy high school athletes not in peak training had elevated serum uric acid values (46). The same results were obtained in a sample of 29 healthy college athletes not in peak condition (20).

Given (a) the association between serum uric acid concentration, gout, and cardiovascular disease, (b) the uncertain role of chronic exercise on serum uric acid values and (c) the growing inclination of physicians to prescribe graded physical exercise as both a preventive measure (65) and a rehabilitation procedure (26), the purpose of this paper is to explore in greater depth the relationship between hyperuricemia and gout and cardiovascular disease including a consideration of hereditary and behavioral factors — with special emphasis on the role of physical exercise.

REVIEW OF HYPERURICEMIA

Hyperuricemia and Gout

In 1876 Garrod (59) observed the blood of gouty patients contained more uric acid than that of normal persons. Since then there has developed a greater understanding of the relationship between hyperuricemia and gout. Seegmiller, *et al.* (59) proposed a working hypothesis to account for several but not all of the steps in the pathogenesis of an acute attack of gouty arthritis: (a) crystals of monosodium urate deposited from hyperuricemic body fluids must be present in the joint tissue, (b) an inflammatory reaction to the crystals must develop and (c) the inflammatory reaction must be propagated by the addition of more urate crystals to the area of inflammation.

The cause of hyperuricemia in gouty patients has not been determined absolutely but there seems to be general agreement that the cause is due to

(a) excessive production of uric acid, (b) normal production but diminished ability of the kidneys to excrete uric acid or (c) a combination of both (37, 48, 57, 58).

It seems important that uric acid levels be maintained as low as possible because Hall, *et al.* (22) found that among those subjects who had serum uric acid levels of 8.0 mg/100 ml or higher, 36% had gouty arthritis and among those who had uric acid levels above 9.0 mg/100 ml, 40% had renal calculi. Among those subjects who had uric acid levels above 12 mg/100 ml, 50% had renal calculi (66).

Regardless of its cause, the level of hyperuricemia is correlated directly with the presence of tophi (59). These tophi can be reduced by administration of uricosuric agents (drugs) that lower the concentration of uric acid in body fluids by promoting its excretion from the kidneys (35). Therefore, two questions are raised regarding exercise: (a) are bouts of acute vigorous exercise contraindicated for individuals with a tendency toward hyperuricemia and (b) what, if any, is the value of carefully controlled chronic exercise in the prevention of hyperuricemia?

Hyperuricemia in Selected Populations

Epidemiological studies have shown that populations vary in mean serum uric acid levels (Table 1) and that frequency distributions are normal in some instances and skewed positively in others (20, 21, 36, 44). Hyperuricemia is more common than gout and both are more common in males than in females (20, 21, 22). For males, the lower limit of "hyperuricemia" is placed generally at about 7.0 mg/100 ml. when measured by the enzymatic spectrophotometric method (40) and urate crystal precipitation is uncommon below this level (59). Uric acid values measured by the colorimetric method are usually 0.2-0.6 mg/100 ml. higher than the enzymatic method (27). Serum uric acid values above 7.0 mg/100 ml. are not uncommon in adult males but are relatively rare in premenopausal women. This observation parallels the known incidence of clinical gout (44). In the same study, 9.2 percent of the male population over 20 years of age were hyperuricemic (above 7.0 mg/100 ml.). This is particularly important in view of the fact that the Framingham Heart Disease study (22) has reported that the risk of gout developing within a 10-year period is approximately one in five for middle-aged men with serum uric acid levels above 7.0 mg/100 ml.

Montoye (46) in a recent study of high school athletes not at peak training, reported elevated serum uric acid values. Greenleaf, *et al.* (20) measured serum sodium urate concentrations in 29 healthy Caucasian male college athletes and found an unexpected number (52 percent) had levels of 6.0 mg/100 ml. or greater and 14 percent had levels of 7.0 mg/100 ml. or greater. Similar data from a group of healthy, physically active women showed no abnormal increase in serum uric acid, (Table 1) whereas the mean of a population of male athletes (20) was significantly higher than that of

Emmerson and Sandilands' (16) "normal" population. The study (20) demonstrated yet another asymptomatic group, college athletes, in whom elevated urates may exist and not necessarily reflect a disease state. Three factors might be identified which, singly or in combination, may have contributed to the high uric acid values in high school and college athletes—acute and/or chronic physical exercise, genetic predisposition and achievement-oriented behavior.

Table I

Comparison of Some Representative Serum Uric Acid Values in Males and Females**

Reference	No. Cases	Occupation Age	Serum Uric Acid Conc. (mg/100 ml) (Mean ±S.D.)	(Range)	(> 5.9)	(> 6.9)
MALES						
Mikkelsen, *et al.* (44) (Americans)	2,987	Various 4-80+	4.9±1.4*	1.0-13.6	20.8	7.4
Mikkelsen, *et al.* (44) (Americans)	153	Various 20-24	5.6±1.3*	2.6-13.6	28.8	11.1
Emmerson, *et al.* (16) (Australians)	100	Students 20-30	5.6±1.0†‡	3.5-8.4	32.0	7.0
Dreyfuss, *et al.* (12) (Israelis)	21 (18 + 3)	Students 20-30	5.4±1.1§	4.1-7.4	33.3	9.5
Dunn, *et al.* (13) (Americans)	331	Executives 40-60	5.7±1.2*	———	43.3	16.5
Dunn, *et al.* (13) (Americans)	76	Ph.D. Scientists	5.3±1.2*	———	26.3	9.2
Dunn, *et al.* (13) (Americans)	532	Craftsmen 40-60	4.8±1.1*	———	12.6	3.5
Greenleaf, *et al.* (20) (Americans)	29	Athletes 21-31	6.1±1.0‡	3.6-11.4	51.7	13.8
FEMALES					(> 4.9)	(> 5.9)
Mikkelsen, *et al.* (44) (Americans)	3,013	Various 4-80+	4.2±1.2*	1.0-11.9	21.9	7.2
Mikkelsen, *et al.* (44) (Americans)	277	Various 25-29	4.0±1.2*	1.0-11.6	16.2	5.4
Emmerson, *et al.* (16) (Australians)	100	Nurses 20-25	4.5±0.7†‡	2.5-6.4	30.0	1.0
Greenleaf, *et al.* (20) (Americans)	11	Physical Education Teachers 24-33	4.6±0.7‡	3.0-6.4	27.3	9.1

*Liddle, *et al. J. Lab. Clin. Med.* 54: 903, 1959. (Enzymatic method)
†Feichtmeir, *et al. Am. J. Clin. Path* 25: 833, 1955. (Enzymatic method)
‡Henry, *et al. Am. J. Clin. Path.* 28: 152, 1957. (Colorimetric method)
§Hepler, *et al. Am J. Clin. Path.* 22: 72, 1952. (Colorimetric method)
**From Greenleaf, *et al. Am. Corr. Ther. J.* 23: 66, 1969.

Hyperuricemia and Heredity

Little is known about the relative role of genetic factors in the control of serum uric acid levels in humans although several studies have suggested inborn differences between various ethnic groups and communities apparently unexplainable by diet, drugs, or other diseases (25, 60, 61). The kind of experimental design used in these studies is typified by that of Hauge and Harvald (25) in which 261 relatives of gouty subjects were compared with 266 relatives on non-gouty matched controls. Their results indicated a clear "familiality" for hyperuricemia, gout, and urinary calculi. Another epidemiological study on Indians in Arizona and Montana concluded, however, that the trait of hyperuricemia is, for the most part, not a genetic one but is largely determined by environmental factors (49). Epidemiological and familial studies have been criticized by Blumberg (3), since they do not differentiate between heredity and environmental factors.

A most comprehensive genetic study was done by Boyle, *et al.* (5) on 112 pairs of male and female twins. They compared the mean intrapair variance of serum uric acid levels in monozygotic (genetically identical) twin pairs and contrasted it with the mean intrapair variance of dizygotic (genetically non-identical) twin pairs. A genetic influence would predominate if the variance between the monozygotic twin pairs were smaller than the variance in the dizygotic pairs. This did indeed occur in the females ($p<.001$). However, just the opposite occurred in the males, i.e., there was a larger but not statistically significant variance in the monozygotes. Their results suggest that in males the mechanisms controlling the normal serum uric acid levels are influenced more by environmental factors whereas in females, hereditary factors predominate. This may account for the greater variation in means and variances reported in male populations (Table 1).

Apparently, no studies have attempted to demonstrate a genetic influence on the elevated serum uric acid levels reported in athletes. Future research should attempt to elucidate exact mechanisms and differentiate between hereditary and environmental factors.

Hyperuricemia and Psycho-social Factors

A number of epidemiological studies have shown significant but low positive correlations between high serum uric acid levels and psycho-social characteristics such as intelligence, *achieved* social status and "drive" (7, 13, 30, 45, 62). A small but statistically significant correlation ($r=0.07$) between serum uric acid levels and intelligence was found in army inductees (62). A positive association between serum uric acid levels and "achieved" social status was observed in students, craftsmen, executives and scientists (13). A positive relationship ($r=0.66$) was shown in university professors, between serum uric acid levels and "drive," achievement and leadership (7). This was the highest correlation coefficient reported between a behavioral variable and serum uric acid. Kasl, *et al.* (30) found higher serum uric acid levels in children who were highly motivated academically. Mon-

toye, *et al.* (45) reported a significantly higher serum uric acid concentration (by 0.5 mg/100 ml) in a subgroup of Michigan business executives compared to comparably aged men from a larger population.

Recently, several researchers have attempted to measure serum uric acid before, during and after psychological and/or physical stress (31, 36, 52, 53). These studies are in general agreement that serum acid concentration rises approximately 0.5 - 1.0 mg/100 ml during periods of *anticipation* of demanding situations but that it falls approximately 0.5 - 2.0 mg/100 ml *during* periods of intense physical and psychological overload. A crucial area of differentiation between persons with high serum uric acid levels and those with elevated serum cholesterol was in how the individual perceived his current life situation. Persons with high serum uric acid concentrations seemed to view current life stresses as enjoyable challenges, while individuals with high cholesterol viewed those stresses as overburdening (31, 36, 52).

The results of these studies appear to support an association between the hyperuricemic state and certain behavior patterns. However, they also suggest that it is still far from clear whether they reflect inherent personal characteristics, environmental factors reflected in a different "style of life," or both. In view of the elevated serum uric acid concentrations reported in athletes out of training, the challenge is to determine if the cause is due to achievement-oriented personality, physical activity, etc.

Hyperuricemia and Cardiovascular Disease

Epidemiological studies of coronary heart disease have identified characteristics which, to some extent, are associated with an increased liability to cardiovascular disease. The Framingham study (22) demonstrates that the predominant factors are high serum lipid patterns, hypertension, obesity, smoking and inactivity. Two metabolic disorders, gout and diabetes, are also postulated as predisposing to coronary heart disease. Therefore, it would seem important to ascertain whether elevated serum uric acid contributes to the development of coronary heart disease, since effective treatment for hyperuricemia by use of drugs is available. For the same reason, it would also be important to know if chronic physical exercise had any preventive or controlling effect on hyperuricemia. By the same token, the hyperuricemic effect of acute exercise (see following section) may contraindicate participation in acute strenuous exercise for hyperuricemic individuals.

Despite the apparent association between obesity and atherosclerosis, studies of relationships between hyperuricemia in individuals with or without gout and atherosclerosis have been undertaken only in recent years. Probably the earliest systematic study of this kind was that of Gertler, *et al.* (18) who found hyperuricemia to be four times as prevalent in a group of 92 men who had suffered a myocardial infarction before the age of 40 than in control subjects. Since then various investigations have demonstrated positive but low correlations between gout and arteriosclerosis (15), myocardial infarction (34), cerebral thrombosis (23), essential hypertension (32), dia-

betes mellitus (64) and familial xanthomatosis (29), all of which (gout excepted) are caused by or associated with atherosclerosis (1).

However, there are many unresolved questions concerning the relationships between the above diseases, hyperuricemia, gout and the various lipids that might influence them. For example, some studies (6, 11, 28, 32, 33), but not all (65) have reported hyperuricemia in hypertensive patients without typical gouty arthritis.

Some investigators have reported a positive correlation between cholesterol and uric acid (35, 56) while others (1, 14) failed to find significant correlations between serum concentrations of either cholesterol or triglyceride and uric acid. It is quite likely these serum fractions vary independently of one another (55).

Finally, a great deal of interest has centered around the positive relationship of obesity and/or weight and hyperuricemia, with several researchers (1, 7, 18, 32) reporting positive but low correlations and others (4, 63) reporting little or no correlation. Probable reasons for confusion in this area may be found in the failure to differentiate clearly between obesity (relative quantity of fat) and absolute body weight. If the association between weight and serum uric acid concentration is a real one, it may contribute to the higher levels found in athletes. Athletes are generally taller and heavier than their non-athletic counterparts (46).

Hyperuricemia and Acute Exercise

Acute exercise is defined as a *single* bout of exercise and its immediate physiological effects.

The experimental studies (39, 41, 47, 51, 54, 67) are practically unanimous in reporting increases in serum uric acid with acute exercise. Researchers reported an increase of 0.9-1.5 mg/100 ml with single bouts of short, strenuous exercise (54); a rise of 0.4-2.6 mg/100 ml following a marathon race (39); a rise of 1.0 mg/100 ml following one half hour of muscular endurance exercises (41); a very small rise (0.2 mg/100 ml) after one hour of exercise (51); a rise of 0.5 mg/100 ml after 30 minutes of running (47) and a slight increase (0.2 mg/100 ml) in serum uric acid in 20 healthy young male subjects who did light muscular exercise for 30 minutes (67).

Neither the causal relationship between muscular exercise and elevated serum uric acid nor the underlying physiological mechanisms have been clarified exactly, but it is accepted generally that the hyperlactacidemia associated with exercise causes a decrease in urinary urate clearance by inducing an increase in tubular reabsorption of urate in the kidneys, resulting in a corresponding rise in its concentration in the blood (47). Further substantiating this argument is the work of Michael (43) who reported a close correlation between *artificially induced* hyperlactacidemia and inhibition of uric acid excretion. However, many other substances have been shown to

inhibit uric acid excretion. For example, uric acid excretion by the kidneys has been inhibited by hyperlipidemia and/or induced ketosis (50).

Hyperuricemia and Chronic Exercise

Chronic exercise (training) is defined as an intermittent series of *single* bouts of exercise (usually progressively strenuous in nature) and their *cumulative* physiological effects. The question of concern is whether the effects of chronic exercise are identical, basically, to those of acute exercise.

The attempts to elucidate the effects of chronic exercise on serum uric acid concentration have resulted in (a) epidemiological studies on athletes (13, 20, 46) wherein the effects of chronic exercise are *implied* and (b) experimental studies (4, 8, 9, 42, 52, 53) wherein the longitudinal effects of training are *observed*.

In the former type of study, Dunn, *et al.* (13) observed a positive relationship in male high school students between serum uric acid and the degree of participation in combined scholastic and athletic activities but no relationship between serum uric acid and athletic participation only. Significantly elevated serum uric acid values (by 0.6 mg/100 ml) were reported in high school athletes (46) and in college athletes (20) not at peak training, suggesting that decreased activity was associated with higher uric acid. In another study, Montoye, *et al.* (45) observed in a group of business executives, a direct relationship between physical activity and serum uric acid. In the most active group, uric acid averaged 6.5 mg and that of the least active was 5.8 mg/100 ml. This seemingly paradoxical relationship between activity levels and serum uric acid levels can be explained if it is assumed that activity levels of relatively sedentary people, i.e., executives, are more closely dependent upon a "drive"-achievement factor, therefore having higher serum uric acid. This would also explain why athletes have higher serum uric acid when out of training — a "drive"-hereditary factor "sets" the resting level but chronic exercise (training) decreases it.

Few studies have attempted to measure uric acid during longitudinal physical training. The results of these studies have been conflicting and confusing. Serum uric acid in Marine recruits did not change at the end of a training period (8) while in a second study, (9) uric acid decreased. Rahe and Arthur (53) noted a decrease of 1.6 mg/100 ml in serum uric acid during underwater demolition training. In a second study Rahe, *et al.* (52) observed statistically significant elevations in serum uric acid when trainees were eagerly performing new and challenging (early in training) strenuous activities, and significant decreases of 0.9 - 1.3 mg/100 ml when the men undertook prolonged, unpleasant activities.

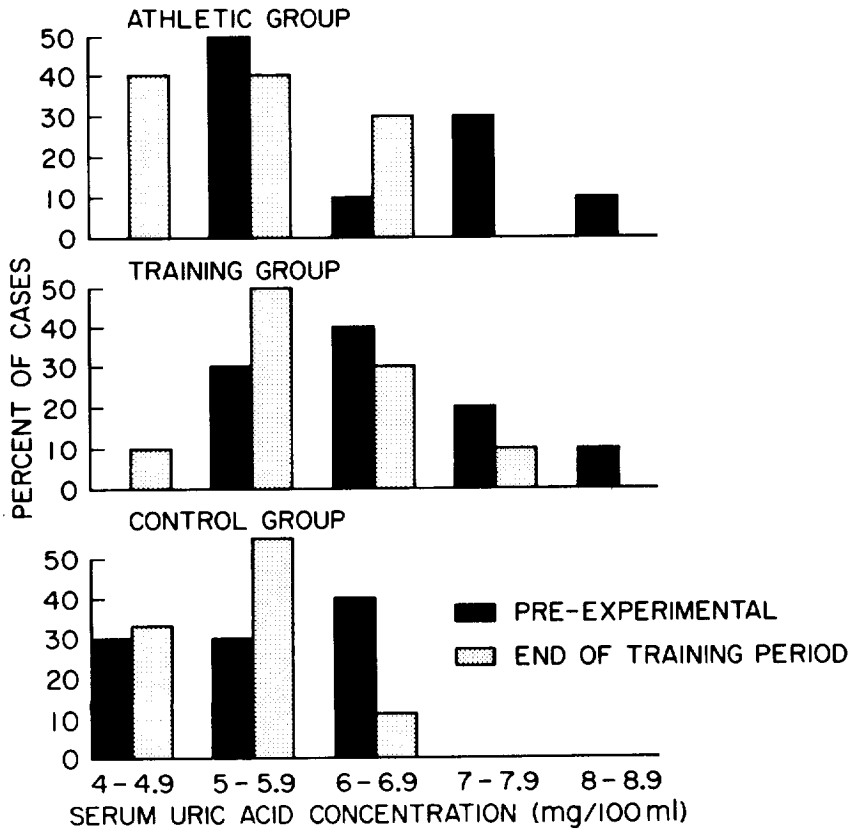
The two most recent studies have reported conflicting results. Mann, *et al.* (42) studied the effects on unfit adult men of six months of physical training consisting of a series of calisthenics with alternate periods of walking, jogging and running. The mean serum uric acid concentration increased slightly (about 0.5 mg/100 ml). They proposed that the increase was due

possibly to an increase in muscle mass of their subjects or to repetitive hyperlactacidemia.

Bosco, *et al.* (4) investigated the effect of eight weeks of chronic exercise on serum uric acid concentration. The sample was composed of 30 normal, healthy, college-aged students: 10 athletes in training (athletic group), 10 moderately active physical education class participants (training group) and 10 relatively sedentary individuals (control group). Serum uric acid concentration was measured at the beginning, periodically during an eight-week training period and after a four-week "deconditioning" period. It was found that chronic physical exercise lowered serum uric acid 0.3 to 3.2 mg/100 ml in 80% of the subjects in the athletic and training groups, particularly in those subjects with initially elevated values of 7.0 - 8.5 mg/100 ml (Fig. 1). Their most important finding was a significant ($p<0.05$) decrease

FIGURE 1.

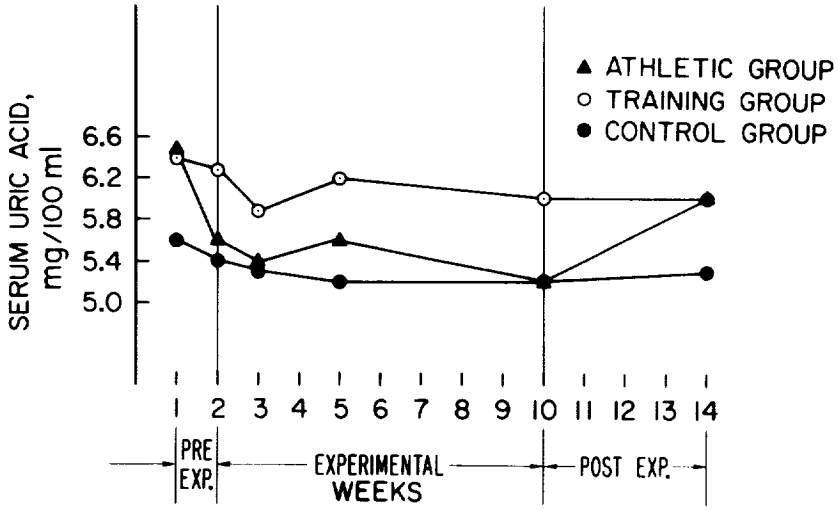
Shift in Serum Uric Acid Concentration after Eight Weeks of Exercise at Three Intensity levels.



in serum uric acid in the athletic group which underwent an extremely strenuous exercise program in comparison to the other groups (Fig. 2).

FIGURE 2.*

Within-group changes in serum uric acid concentration. The uric acid values at the end of the experiment (training) period are compared with the pre-experimental values.



*From Bosco, et al. Amer. J. Cardiol. 25: 47, 1970.

Factors which could have contributed to the lowering of serum uric acid concentration with chronic exercise (training) were classified (4) as follows: (A) *primary* effects on uric acid metabolism *per se* due to exercise stimuli, and (B) *secondary* reactions of uric acid due to the effects of exercise on some other variable, e.g., lipid or amino acid metabolism. The *primary* effects were: (a) a decrease in uric acid production with constant excretion, (b) an increased excretion with constant production, (c) no change in uric acid turnover rate, but a progressively increasing plasma volume and (d) some influence of diurnal and/or seasonal variations on uric acid metabolism. The two most likely *primary* effects explaining lowering of serum uric acid during chronic exercise (training) were: (a) a relatively constant turnover of urate accompanied by a progressively increasing plasma volume and (b) an absolute increase in urinary uric acid excretion. The failure of Calvy, *et al.* (8, 9) and Mann, *et al.* (42) to obtain a decrease in serum uric acid concentration with chronic exercise (training) may have been due to the high fat diet used by Calvy's subjects and the increase in fat intake by Mann's subjects which would tend to decrease uric acid excretion (50) thereby maintaining higher blood levels. More complete answers await the research that will, in one study (a) control dietary intake, (b) control the amount of

exercise and (c) measure serum uric acid concentration, plasma volume, and urinary excretion of uric acid.

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